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Developmental immune activation programs adult behavior: insight from research on birds

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Abstract

Immune activation early in life can program adult behavioral expression. Previous research on birds has documented effects of parasite exposure and immune challenges early in life on dispersal, song, personality, learning and feather pecking. However, the mechanisms responsible for mediating these programming effects are unknown. Candidate brain regions that may be most sensitive include the hippocampus and HVC. Without an understanding of mechanism, it is difficult to assess if programmed behaviors represent pathological side effects or behavioral modifications with benefits to either hosts or parasites. Future research on birds promises to provide novel insight into the adaptive value of programming effects of early life immune activation and the capacity for selection to buffer hosts against negative effects.

Introduction

Adult behavioral expression is a product of genetic and environmental influences and interactions between an individual's genotype and its environment. In particular, the early life environment may exert persistent effects on behavioral expression that constrain the range of behavioral phenotypes expressed in adulthood [1,2*]. For example, exposure to stressors during critical developmental windows early in life may program adult behavioral expression. Stressors that have been demonstrated to influence adult behavior in birds include nutritional stress [2*,3,4,5], brood size [6], and parasite exposure or immune challenge [7,8,9,10]. Birds are an excellent group in which to study programming effects of early life immune activation on behavior because behavior can be readily observed under natural conditions and is well characterized for many species from diverse habitats and with divergent life history strategies. This greatly enhances our ability to assess the adaptive value of behavioral modifications. Early life infection can also be readily manipulated both in nests in the field and in the lab. Moreover, the neural basis of fitness-linked behaviors in birds such as song and food caching are well described. This enhances our ability to map the mechanisms connecting early life infection to adult behavior. However, despite good evidence for persistent effects of maternal and developmental environments on adult phenotype in birds [11*,12], we still know relatively little about the fitness consequences of

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early immune activation and the mechanisms that underlie behavioral and cognitive consequences. Here, I will first highlight existing research demonstrating that immune activation early in life may program adult behavior. I will then discuss proximate mechanisms that may link early life immune activation with adult behavior. My aim is to stimulate new research in this area and thus, I conclude by proposing hypotheses to be tested in future work.

Adult behaviors programmed by early life immune activation

Dispersal

Ectoparasites, such as mites, fleas, bugs, and ticks, can build up to large numbers in bird nests during breeding and may significantly depress nestling body mass and survival [13]. Early experience with parasitism influences dispersal behavior in a number of species [14,15]. Brown and Brown [16] were the first to demonstrate that the level of exposure to nest ectoparasites influenced natal dispersal distance in the cliff swallow (*Petrochelidon pyrrhonota*). Both within and among cliff swallow colonies there is substantial variation among nests in numbers of the swallow bug (*Oeciacus vicarius*). Swallows that were raised in nests with swallow bugs dispersed greater distances than swallows raised in nests without swallow bugs [16]. By increasing dispersal distance, swallows may be better able to avoid parasitized sites. Conversely, nestling great tits (*Parus major*) exposed to hen fleas (*Ceratophyllus gallinae*) in the nest disperse shorter distances than non-parasitized birds [7,14], but again this behavioral change is adaptive. Birds from nests with hen fleas achieve lower reproductive success if they disperse longer distances, whereas birds from parasite-free nests attain higher reproductive success by dispersing greater distances [7]. This change in dispersal behavior as a result of exposure to ectoparasites seems to be maternally mediated. Females with hen fleas in their nests produce eggs with lower androgen concentrations [17], and if egg androgen concentrations are experimentally increased, offspring disperse greater distances [7]. However, the proximate mechanisms that link androgen concentration in the egg to natal dispersal distance have not yet been elucidated.

Song

Exposure to stressors early in life can disrupt development of the song control system in songbirds and impair the quality of adult song. Thus, male song is an honest indicator to potential female mates of a male's quality and exposure to stress during development. This is known as the developmental stress hypothesis [18,19]. Although early tests of the hypothesis focused on the effects of nutritional stress early in life, a few studies have also demonstrated that parasitism in early life can affect both neural development and male song. Canaries (*Serinus canaria*) experimentally infected with avian malaria (*Plasmodium relictum*) during the growth period of the primary nuclei in the song control system sang simpler songs as adults and the volume of one song control nucleus, the HVC, was significantly smaller [20]. Similarly, in a wild population of great tits, experimental manipulation of hen flea infestation during the nestling period affected male song up to several years later. Males reared in parasitized nests sang shorter songs in response to playback song of a simulated intruder and overlapped their song less with the playback [8]. In this population, females also laid more eggs when mated to a male with a longer song

response to the playback [8]. Thus, parasite exposure in early life may reduce fitness by decreasing male attractiveness and competitiveness in adulthood.

Personality

Adult personality traits may reflect, in part, activation of the immune response during development. Infection can alter host state, which includes traits such as energetic reserves and reproductive potential [21]. Because state characters influence the adaptive value of behaviors, personality differences may be at least partially due to variation among hosts in state as a function of infection history or susceptibility to infection [21,22,23]. To test this hypothesis, mallard ducklings (*Anas platyrhynchos*) were immune challenged during one of three phases of development, and activity and exploration in a novel environment and response to novel objects of different colors were quantified in adulthood after a subsequent immune challenge [9]. Initial immune challenges administered after completion of somatic growth, but before completion of molt into the nuptial plumage, increased activity in adulthood and altered color-based novel object exploration, but did not influence overall exploratory behavior [9]. A study of zebra finches (*Taeniopygia guttata*) assessed the potential for both maternal and developmental immune challenges to impact neophobia in adulthood measured as response to novel objects. Mothers were given two immune challenges prior to egg production. Offspring were either challenged with the same or a different antigen from mothers twice in the first month post-hatch [10]. Neophobia in adult offspring was significantly impacted by an interaction between maternal treatment, offspring treatment, and offspring sex such that developmentally immune challenged males whose mothers had not been challenged with the same antigen exhibited the least neophobia [10]. This demonstrates that immune activation may have sex-specific effects on behavior. Both of these studies support the hypothesis that immune activation early in life may underlie some of the variation in adult personality.

Learning

Activation of the immune response early in life impairs learning and memory in rodents [24]. One study found a similar effect in birds. Male zebra finches challenged with the endotoxin lipopolysaccharide (LPS) early in life exhibited reduced performance on a novel foraging task when tested approximately one year later, whereas female performance was not impacted by this endotoxin challenge [10]. As with the effects of immune challenge on neophobia, this demonstrates that immune activation may have sex-specific effects on behavior and future research should explicitly test for sex differences [25].

Feather pecking

Feather pecking and other forms of damaging pecking are a major animal welfare concern, especially in chickens housed in large groups [26]. There is significant variation in both the occurrence and intensity of pecking, but the physiological mechanisms responsible are unknown [27]. A role for the immune system in feather pecking is plausible because selection lines of white leghorn chickens with high levels of feather pecking also have strong humoral immune responses [28]. Furthermore, young, group-housed birds challenged with a novel antigen suffered more feather damage months after exposure than

unchallenged, group-housed birds [29]. Thus, activation of the specific, humoral immune response during critical windows early in life may be at least partially responsible for this damaging behavior [29].

How does immune system activation early in life program adult behavior?

Very little work in birds has investigated the mechanisms linking immune system activation in early life with adult behavioral expression. However, research on mammalian model systems provides potential proximate mechanisms that may link early life immune activation with adult behavior in birds. Two candidate brain regions that may be both most susceptible to the effects of immune activation and, which may subsequently result in measurable changes in behavior are the hippocampus and the HVC. In both birds and mammals, the hippocampus is particularly sensitive to stressors early in life, including immune activation [30,31]. Given that the hippocampus is critical to spatial learning and memory [32], some of the effects of immune activation on learning [10] and dispersal [7,16] may be mediated by effects on this structure. In oscine songbirds, the HVC is important for song learning and complex song production. Notably, both brain regions exhibit decreased volume and neuronal number after stress exposure [33**].

Both the hippocampus and HVC exhibit remarkably high levels of neuroplasticity: the propensity for environmental challenges and enrichment to result in neuronal and synaptic changes [33**]. Although the capacity for neuroplasticity plays a critical role in facilitating learning and memory processes in these brain regions, it may also increase vulnerability to stressors, including immune challenge [33**,34,35]. Properties common to the hippocampus and HVC that may convey sensitivity to stressors such as immune activation include extended periods of neurogenesis [36], high densities of glucocorticoid receptors [37], and dependence on cytokines and chemokines for normal development [35,38]. Because of the extended period of neurogenesis in these two brain regions, there is a longer period of time during which infection may inhibit neurogenesis [39**].

Exposure to stressors stimulates the hypothalamic-pituitary-adrenal (HPA) axis and results in the eventual production of glucocorticoid hormones, including corticosterone, the primary glucocorticoid hormone in birds. Glucocorticoid receptors are distributed widely in the songbird brain, including in the hippocampus and HVC [37]. Glucocorticoids are necessary for normal brain development, but exposure to excessive levels is detrimental [40,41]. The enrichment of glucocorticoid receptors in the hippocampus and HVC is relevant for the study of the mechanisms linking developmental immune challenges with adult behavioral expression because infection often activates both the immune response and the HPA axis simultaneously [39**] (Fig. 1). Thus, the presence of glucocorticoid receptors in the hippocampus and HVC means that elevated glucocorticoid levels produced after infection may directly affect these brain regions. Furthermore, maternal and developmental immune challenges can change the sensitivity of offspring to non-immune stressors in adulthood [42**]. This long-term change in corticosterone production after early life immune activation may be a result of changes in glucocorticoid receptor expression [43] that are stably maintained through epigenetic effects with consequences for behavior [44]. Future

research on birds should address how changes in glucocorticoid receptor expression may convey resilience during critical developmental windows [33**].

Cytokines and chemokines are immune signaling molecules that facilitate communication with the endocrine and nervous systems [35,45]. They are required for normal mammalian brain development and may enhance hippocampal plasticity through modulation during learning [41], but because exposure to elevated levels induced by central or peripheral infection or injury can result in pathological effects, cytokines and chemokines may also enhance hippocampal susceptibility [24,35]. It is widely recognized that cytokines are responsible for triggering rapid behavioral changes after infection (i.e., sickness behaviors) [46], but they may also be important for triggering long-term changes in behavior after early life infection by increasing reactivity of the neuroimmune system to subsequent infections [24] (Fig. 1). Future research on birds should address the potential for cytokines induced by early life infection to program adult behavior.

Pathology or adaptive behavioral modification?

When immune system activation early in life programs adult behavioral expression, this effect may either represent a pathological side effect or it may represent a behavioral modification with benefits to either the host or the parasite [21]. In the evolutionary arms race between hosts and parasites, hosts evolve mechanisms to defend against infection and parasites evolve mechanisms to circumvent host defenses and ensure transmission. For parasites that are transmitted through social contact, host behavioral modifications to increase social behaviors should enhance transmission [47], whereas parasites dependent on predation for transmission may decrease neophobia and increase exploratory behaviors of hosts [47,48]. Thus some programming effects of early life infection may result from parasite-mediated manipulation of host behavior. The best-studied example of this results from infection with the protozoan parasite *Toxoplasma gondii* [48]. Rats infected with *T. gondii* approach cat odors, have increased activity, decreased neophobia, and decreased anti-predator vigilance [48]. These behavioral changes increase the likelihood of predation by cats, which are the definitive host for *T. gondii*. Although birds may also be intermediate hosts, studies have not addressed behavioral effects of infection [49]. Parasite modification of host behavior often involves modification of a suite of behaviors by parasites that co-opt integrated pathways between behavior and immunity to increase the likelihood of transmission [50]. It can be difficult to distinguish whether behavioral changes after infection are a pathological side effect or an active modification of behavior by parasites without a detailed understanding of the mechanisms linking infection and behavior and the mechanisms linking behaviors to one another [50].

As outlined above, cytokines trigger sickness behaviors such as anorexia, lethargy, and somnolence after infection [46]. These behavioral changes help hosts survive infection [51]. Although most biomedical literature focuses on the negative psychological effects of early life immune activation, programmed behavioral changes may also be adaptive. For example, altered dispersal distances and changes in neophobia may help hosts avoid re-infection. Thus, it is important to assess the adaptive value of programmed behavior after early life immune activation in natural settings.

Selection for resilience against the effects of immune system activation on behavior

Given the sensitivity of the hippocampus and HVC to stress exposure, including immune activation, there should be strong selection for resilience against pathological effects, particularly in species where behaviors mediated by the hippocampus and HVC are tightly linked with fitness [33**]. However, resilience may be constrained by the inherent plasticity in the hippocampus and HVC that is required to allow ongoing, experience-dependent changes in synaptic and dendritic morphology and adult neurogenesis [33**]. If selection for neuroplasticity constrains selection for resilience, then selection may instead favor behavioral and physiological mechanisms in parents and offspring to reduce the risk of infection during critical periods early in life [52*] (Fig. 2).

Future directions

Few studies have investigated programming effects of early life immune activation on behavior in birds. Thus, we first need additional studies in which parasite exposure or immune challenge are experimentally manipulated during the nestling period and behavioral phenotypes are quantified from the same individuals in adulthood, ideally in species inhabiting different environments and with divergent life history strategies. Second, the mechanisms that link early life immune activation and adult behavior are almost completely unknown in birds. Candidate brain regions that may be of central importance include the hippocampus and HVC. Programming effects on behavior may then be mediated through changes in glucocorticoid receptor expression [33**] or priming effects of cytokines on the neuroimmune response [24]. Research to address mechanisms that parents and offspring may employ to minimize the effects of infection during critical developmental windows is needed [53] (Fig. 1), as well as comparative studies to determine if these mechanisms are more widespread in species with strong selection for cognition [33**] (Fig. 2). For example, the production of learned vocalizations has arisen independently three times within birds, in hummingbirds, parrots, and oscine songbirds. These three groups of birds are predicted to exhibit convergence in resilience in the brain regions responsible for song learning and production or convergence in avoidance of infection. Similarly, birds dependent on caching behavior or that migrate long distances may experience strong selection for resilience and infection avoidance. Within a species, there may be stronger selection to avoid infection during the song learning period on males than on females in species in which only males sing (Fig. 3). The relative costs and benefits of engaging in infection avoidance behaviors should also change with age. For young birds with naïve immune systems, there should be strong benefits of behavioral avoidance strategies during critical windows of brain development. Conversely, for middle-aged birds with prior infection exposure, the costs of avoiding conspecifics may outweigh any benefits. Finally, later in life, the benefits associated with activating the immune response diminish as the immune system senesces and costs increase as individuals become more susceptible to overactive inflammatory processes, and older individuals should instead rely on avoidance behaviors [54,55] (Fig. 4). Future research in birds promises to provide novel insight into the adaptive value of

programming effects on behavior and the capacity for selection to favor mechanisms of resilience and avoidance to buffer against programming effects.

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Highlights

- Immune activation early in life programs adult behavior
- Behaviors programmed in birds include: dispersal, song, learning, and personality
- The hippocampus and HVC may be most sensitive to immune activation
- Glucocorticoids and cytokines may play important roles in programming
- Selection should favor resilience or infection avoidance early in life

Figure 1.

Diagrammatic representation of pathways through which maternal and developmental infections may program offspring behavior in adulthood. Maternal infection activates the maternal immune response and stimulates transmission of maternal antibodies and antimicrobial proteins. These egg components may alter the offspring immune response and provide protection against infection. Maternal infection also stimulates the stress response of mothers and may alter maternal behavior. Changes in maternal behavior may then influence offspring brain development. Offspring infection stimulates the immune and stress responses of offspring with consequences for brain development and adult behavioral expression. Parents may protect offspring from infection by avoiding areas with parasites, utilizing nest materials that reduce viability of parasites, and preening offspring. For figure clarity, I have not included all possible pathways.

Figure 2.

Predicted relationship across species between reliance on complex song production or spatial memory ability to achieve high fitness and the occurrence of adaptations to minimize costs of infection early in life. Adaptations may confer resilience after infection by, for example, down-regulating glucocorticoid receptor expression or reducing sensitivity to the effects of cytokines and chemokines. Alternatively, adaptations may help hosts avoid infection.

Figure 3.

Predicted sex difference in infection avoidance behaviors during the period of song system development in species in which only males learn complex songs.

Figure 4.

Predicted variation across the lifespan within a species in the expression of costly infection avoidance behaviors. Avoidance behaviors are expected to be most common in young and old individuals. Young individuals with immature, naïve immune systems may benefit most from avoidance behaviors during critical periods of brain development. Older individuals may also express avoidance behaviors to avoid collateral damage to the brain during infection late in life; however, selection in this age group is predicted to be weaker than on young individuals. For middle-aged individuals with mature immune systems, the social costs of avoidance behaviors may outweigh potential benefits.